Stage-Specific Roles for Tet1 and Tet2 in DNA Demethylation in Primordial Germ Cells.

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Authors: John J Vincent, Yun Huang, Pao-Yang Chen, Suhua Feng, Joseph H Calvopina, Kevin Nee, Serena A Lee, Thuc Le, Alexander J Yoon, Kym Faull, Guoping Fan, Anjana Rao, Steven E Jacobsen, Matteo Pellegrini, Amander T Clark

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Public Summary:
Birth of healthy children is dependent upon the correct transmission of DNA through the parents egg and sperm. In this work we used embryonic stem cells as a research model to differentiate immature progenitor sperm cells and discovered that DNA in these cells undergoes two unique phases of covalent change that removes methylated cytosine from DNA. We determined that the second phase of demethylation was dependent upon proteins called Tet methyl cytosine dioxygenases. Results from this work help us to understand and model for the first time how to prevent disease epialleles from being passed on to our future generations.

Scientific Abstract:
Primordial germ cells (PGCs) undergo dramatic rearrangements to their methylome during embryogenesis, including initial genome-wide DNA demethylation that establishes the germline epigenetic ground state. The role of the 5-methylcytosine (5mC) dioxygenases Tet1 and Tet2 in the initial genome-wide DNA demethylation process has not been examined directly. Using PGCs differentiated from either control or Tet2(-/-); Tet1 knockdown embryonic stem cells (ESCs), we show that in vitro PGC (iPGC) formation and genome-wide DNA demethylation are unaffected by the absence of Tet1 and Tet2, and thus 5-hydroxymethylcytosine (5hmC). However, numerous promoters and gene bodies were hypermethylated in mutant iPGCs, which is consistent with a role for 5hmC as an intermediate in locus-specific demethylation. Altogether, our results support a revised model of PGC DNA demethylation in which the first phase of comprehensive 5mC loss does not involve 5hmC. Instead, Tet1 and Tet2 have a locus-specific role in shaping the PGC epigenome during subsequent development.